TITLE OF THE INVENTION

PROCESS FOR THE SYNTHESIS OF AN ENDOTHELIN RECEPTOR ANTAGONIST

FIELD OF THE INVENTION

The present invention is directed to a process for preparing an endothelin receptor antagonist in a practical and efficient way.

BACKGROUND OF THE INVENTION

The endothelin antagonist compound possessing a high affinity for at least one of two receptor subtypes are responsible for the dilation of smooth muscle, such as blood vessels or in the trachea. The endothelin antagonist compounds provide a potentially new therapeutic target, particularly for the treatment of hypertension, pulmonary hypertension, Raynaud's disease, acute renal failure, myocardial infarction, angina pectoris, cerebral infarction, cerebral vasospasm, arteriosclerosis, asthma, gastric ulcer, diabetes, restenosis, prostatauxe endotoxin shock, endotoxin-induced multiple organ failure or disseminated intravascular coagulation, and/or cyclosporin-induced renal failure or hypertension.

Endothelin is a polypeptide composed of amino acids, and it is produced by vascular endothelial cells of human or pig. Endothelin has a potent vasoconstrictor effect and a sustained and potent pressor action (*Nature*, 332, 411-415 (1988)).

Three endothelin isopeptides (endothelin-1, endothelin-2 and endothelin-3), which resemble one another in structure, exist in the bodies of animals including human, and these peptides have vasoconstriction and pressor effects (*Proc. Natl. Acad. Sci.*, USA, 86, 2863-2867 (1989)).

As reported, the endothelin levels are clearly elevated in the blood of patients with essential hypertension, acute myocardial infarction, pulmonary hypertension, Raynaud's disease, diabetes or atherosclerosis, or in the washing fluids of the respiratory tract or the blood of patients with asthmaticus as compared with normal levels (*Japan J. Hypertension*, 12, 79, (1989); *J. Vascular medicine Biology*, 2, 207 (1990); *Diabetologia*, 33, 306-310 (1990); *J. Am. Med. Association*, 264, 2868 (1990); and *The Lancet*, ii, 747-748 (1989) and ii, 1144-1147 (1990)).

Further, an increased sensitivity of the cerebral blood vessel to endothelin in an experimental model of cerebral vasospasm (*Japan. Soc. Cereb. Blood*

Flow & Metabol., 1, 73 (1989)), an improved renal function by the endothelin antibody in an acute renal failure model (*J. Clin. Invest.*, 83, 1762-1767 (1989), and inhibition of gastric ulcer development with an endothelin antibody in a gastric ulcer model (*Extract of Japanese Society of Experimental Gastric Ulcer*, 50 (1991)) have been reported. Therefore, endothelin is assumed to be one of the mediators causing acute renal failure or cerebral vasospasm following subarachnoid hemorrhage.

Further, endothelin is secreted not only by endothelial cells but also by tracheal epithelial cells or by kidney cells (*FEBS Letters*, 255, 129-132 (1989); and *FEBS Letters*, 249, 42-46 (1989)).

Endothelin was also found to control the release of physiologically active endogenous substances such as renin, atrial natriuretic peptide, endothelium-derived relaxing factor (EDRF), thromboxane A_2, prostacyclin, noradrenaline, angiotensin II and substance P (*Biochem. Biophys. Res. Commun.*, 157, 1164-1168 (1988); *Biochem. Biophys. Res. Commun.*, 155, 20 167-172 (1989); *Proc. Natl. Acad. Sci.* USA, 85 1 9797-9800 (1989); *J. Cardiovasc. Pharmacol.*, 13, S89-S92 (1989); *Japan J. Hypertension*, 12, 76 (1989); and *Neuroscience Letters*, 102, 179-184 (1989)). Further, endothelin causes contraction of the smooth muscle of gastrointestinal tract and the uterine smooth muscle (*FEBS Letters*, 247, 337-340 (1989); *Eur. J. Pharmacol.*, 154, 227-228 (1988); and *Biochem. Biophys. Res. Commun.*, 159, 317-323 (1989)). Further, endothelin was found to promote proliferation of rat vascular smooth muscle cells, suggesting a possible relevance to the arterial hypertrophy (*Atherosclerosis*, 78, 225-228 (1989)). Furthermore, since the endothelin receptors are present in a high density not only in the peripheral tissues but also in the central nervous system, and the cerebral administration of endothelin induces a behavioral change in animals, endothelin is likely to play an important role for controlling nervous functions (*Neuroscience Letters*, 97, 276-279 (1989)). Particularly, endothelin is suggested to be one of mediators for pain (*Life Sciences*, 49, PL61-PL65 (1991)).

Internal hyperplastic response was induced by rat carotid artery balloon endothelial denudation. Endothelin causes a significant worsening of the internal hyperplasia (*J. Cardiovasc. Pharmacol.*, 22, 355-359 & 371-373(1993)). These data support a role of endothelin in the pathogenesis of vascular restenosis. Recently, it has been reported that both ET_A and ET_B receptors exist in the human prostate and endothelin produces a potent contraction of it. These results suggest the possibility

that endothelin is involved in the pathophysiology of benign prostatic hyperplasia (*J. Urology*, 151, 763 - 766(1994); *Molecular Pharmocol.*, 45, 306-311 (1994)).

On the other hand, endotoxin is one of potential candidates to promote the release of endothelin. Remarkable elevation of the endothelin levels in the blood or in the culture supernatant of endothelial cells was observed when endotoxin was exogenously administered to animals or added to the culture endothelial cells, respectively. These findings suggest that endothelin is an important mediator for endotoxin-induced diseases (*Biochem. Biophys. Commun.*, 161, 1220-1227 (1989); and *Acta Physiol. Scand.*, 137, 317-318 (1989)).

Further, it was reported that cyclosporin remarkably increased endothelin secretion in the renal cell culture (LLC-PKL cells) (*Eur. J. Pharmacol.*, 180, 191-192 (1990)). Further, dosing of cyclosporin to rats reduced the glomerular filtration rate and increased the blood pressure in association with a remarkable increase in the circulating endothelin level. This cyclosporin-inducea renal failure can be suppressed by the administration of endothelin antibody (*Kidney Int.*, 37, 1487-1491 (1990)). Thus, it is assumed that endothelin is significantly involved in the pathogenesis of the cyclosporin-induced diseases. Such various effects of endothelin are caused by the binding of endothelin to endothelin receptors widely distributed in many tissues (*Am. J. Physiol.*, 256, R856-R866 (1989)).

It is known that vasoconstriction by the endothelin is caused via at least two subtypes of endothelin receptors (*J. Cardiovasc. Pharmacol.*, 17 (Suppl.7), S119-SI21 (1991)). One of the endothelin receptors is ET_A receptor selective to ET-1 rather than ET-3, and the other is ET_B receptor equally active to ET-1 and ET-3. These receptor proteins are reported to be different from each other (*Nature*, 348, 730-735 (1990)).

These two subtypes of endothelin receptors are differently distributed in tissues. It is known that the ET_A receptor is present mainly in cardiovascular tissues, whereas the ET_B receptor is widely distributed in various tissues such as brain, kidney, lung, heart and vascular tissues.

Substances that specifically inhibit the binding of endothelin to the endothelin receptors are believed to antagonize various pharmacological activities of endothelin and to be useful as a drug in a wide field. Since the action of the endothelin is caused via not only the ET_A receptor but also the ET_B receptor, novel non-peptidic substances with ET receptor antagonistic activity to either receptor subtype are desired to block activities of the endothelin effectively in various diseases.